

AWARD NUMBER: W81XWH-15-2-0020

TITLE: Brain MR Spectroscopy Biomarkers in a Clinical Trial of PTS Patients With Comorbid AUD

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CONTRACTING ORGANIZATION: Northern California Institute for Research
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14. ABSTRACT This human neuroimaging application builds on the successful high-field neuroimaging program under the umbrella of the longstanding collaboration between the DoD and the Northern California Institute for Research and Education (NCIRE), carried out jointly by investigators of the Center for Imaging of Neurodegenerative Diseases (CIND) and treatment staff from the VA Mental Health Services. Our overall goal is to determine if topiramate facilitates functionally significant adaptive modulation of •-aminobutyric acid (GABA) and glutamate levels in the neocortex of 40 alcohol dependent veterans with posttraumatic stress disorder (PTSD). We propose to perform longitudinal proton magnetic resonance spectroscopy (1H MRS) as an addendum to an ongoing double-blind placebo controlled trial of topiramate in the treatment of alcohol dependence in veterans with PTSD. Longitudinal control studies will be conducted in 10 healthy controls. All studies will be performed on a 3T scanner and half the sample will also be scanned on the new 7T scanner to assess its utility in patient research.					
15. SUBJECT TERMS Neuroimaging, brain, longitudinal, magnetic resonance spectroscopy, alcohol dependence, posttraumatic stress disorder (PTSD), topiramate, •-aminobutyric acid (GABA), glutamate, US veterans					
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1. INTRODUCTION

This human neuroimaging application builds on the successful high-field neuroimaging program under the umbrella of the longstanding collaboration between the DoD and the Northern California Institute for Research and Education (NCIRE), carried out jointly by investigators of the Center for Imaging of Neurodegenerative Diseases (CIND) and treatment staff from the VA Mental Health Services. In this phase of the collaboration, our overall goal is to determine if topiramate facilitates functionally significant adaptive modulation of γ -aminobutyric acid (GABA) and glutamate levels in the neocortex of alcohol dependent veterans with posttraumatic stress disorder (PTSD). We propose to perform longitudinal proton magnetic resonance spectroscopy (^1H MRS) as an addendum to an ongoing controlled trial of topiramate in the treatment of alcohol dependence in veterans with PTSD.

2. KEYWORDS

Neuroimaging, brain, longitudinal, magnetic resonance spectroscopy, alcohol dependence, posttraumatic stress disorder (PTSD), topiramate, γ -aminobutyric acid (GABA), glutamate, US veterans

3. ACCOMPLISHMENTS

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Generally, the goals will not change from one reporting period to the next and are unlikely to change during the final reporting period. However, if the awarding agency approved changes to the goals during the reporting period, list the revised goals and objectives. Also explain any significant changes in approach or methods from the agency approved application or plan.

We will pursue the following specific aims:

- 1) To measure at 3T cortical metabolite concentrations and their changes in relation to the expected reduced PTS symptom severity, alcohol use, and alcohol craving in dual-diagnosed patients treated with topiramate.
- 2) To determine if topiramate-related cognitive deficits at follow-up are associated with cortical metabolite concentrations measured at 3T.
- 3) To implement at 7T localized quantitative GABA and Glu MRS measurements focused specifically on neocortical and hippocampal gray matter.
- 4) To measure at 7T prefrontal and hippocampal GABA, Glu, and NAA changes during treatment and to compare the detection sensitivity of metabolite change at both field strengths.

Accordingly, the approved SOW is as follows:

Major Tasks as specified in proposal	Timeline	Current status
Major Task 1: Initiate Study	Months	
1a. Obtain local and DoD IRB approval	1-3	completed
1b. Implement and test 7T GABA sequence	1-3	Not finalized
1c. Set up study data base	1-3	completed
<i>Milestone(s) Achieved</i>		
Local and DoD IRB approval	3	Obtained March 2015
Finalize 7T sequences	3	Not finalized
Finalize study data base	3	Completed July 2015
Major Task 2: Conduct Data Acquisition		
2a. Recruit and enroll study participants, and obtain MR data at 3T	4-27	ongoing
2b. Recruit and enroll study participants, and obtain MR data at 7T	4-27	Not started
<i>Milestone(s) Achieved:</i>		
Complete data acquisition at 3T	27	Not completed
Complete data acquisition at 7T	27	Not completed
Major Task 3: Conduct Data Analysis		
3a. Process 3T MRI and MRS data	4-30	ongoing
3b. Process 7T MRI and MRS data	4-30	Not initiated
3c. Break study blind and analyze data	28-33	Not done
<i>Milestone(s) Achieved:</i>		
Finalize 3T MR data analysis	33	Not finalized
Finalize 7T MR data analysis	33	Not done
Major Task 4: Finalize, disseminate, and futurize		
4a. Write final report and manuscripts	28-36	Not started
4b. Disseminate results in research communities	28-36	Not started
4c. Prepare MR data for DataShare	28-36	Not started
4d. Apply for future funding	28-36	Not done
<i>Milestone(s) Achieved:</i>		
Publish ms on 7T data	34	Not done
Complete final report and publish ms on 3T data	36	Not done

What was accomplished under these goals?

Major activities involved around getting the new study off the ground. We obtained both DoD and UCSF/VA IRB approval for the studies, set up the study data base, and established procedures between the parent clinical trial and our neuroimaging component to channel clinical trial participants into this neuroimaging study.

After IRB approval, studies were initiated on the 3T scanner as planned and studies continue to be conducted according to the approved SOW and research proposal.

We started implementing, testing, and optimizing necessary MR spectroscopy pulse sequences on the 7T scanner on both phantoms and normal human research volunteers, when we had to stop our activities because of the expiration of our service contract for the equipment (that was in Fall 2015). As of today, no new service contract was put into place, so that no studies could be performed on the 7T scanner at all between Fall 2016 and today. It is expected that a new service contract between the VA (that owns the equipment) and Siemens (the manufacturer of the equipment) will be in place by July 1, 2016, at which time we will focus on getting the necessary 7T MRS sequences on line and properly tested for patient research.

At 3T, we continued to use our GABA pulse sequence in neuroimaging study participants together with the other MR sequences as specified in the application (note: according to the approved SOW, while all research participants will be scanned at 3T ($n = 50$), only half the participants will be scanned at 7T, $n = 25$).

Within the last year, we screened 13 potential study participants and enrolled/recruited 12 participants, all of whom have gone through the baseline assessments: Of these, 5 participants are pending follow-up MR study; 4 participants were successfully scanned at baseline and follow-up; 1 participant was lost to follow-up after baseline MR; 1 participant was unable to tolerate the full scan at baseline and, thus, was not asked to return for a follow-up scan; and 1 other participant was excluded from the clinical trial after completing the baseline MR exams.

We had hoped that by the end of the first year, we would have enrolled 19 research participants. Efforts are being made to increase enrollments (e.g., changes to inclusion/exclusion criteria).

At this stage, there are no results or key outcomes.

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Dr. Donna Murray is a postdoctoral researcher who has effort on this project. As such, she receives training by the PI on clinical research activities and conduct, including regulatory

work and neuroimaging. She performs the neuroimaging studies and analyses associated with this project. As her primary mentor, I spend several hours during the week on one-on-one training and instructions with Dr. Murray.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

If this is the final report, state "Nothing to Report."

We will continue enrolling research participants into the study as described in the SOW and scan them at 3T. As soon as a service contract is again available for the 7T (expected to be July 1, 2016), we will continue to finalize the 7T MRS sequences to be used in this research.

4. IMPACT

This component is used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period.

No impact worth mentioning yet.

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

5. CHANGES/PROBLEMS:

The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

We started implementing, testing, and optimizing necessary MR spectroscopy pulse sequences on the 7T scanner on both phantoms and normal human research volunteers, when we had to stop our activities because of the expiration of our service contract for the equipment (that was in Fall 2015). As of today, no new service contract was put into place, so that no studies could be performed on the 7T scanner at all between Fall 2016 and today. It is expected that a new service contract between the VA (that owns the equipment) and Siemens (the manufacturer of the equipment) will be in place by July 1, 2016, at which time we will focus on getting the necessary 7T MRS sequences on line and properly tested for patient research.

Recruitment into this neuroimaging component is critically dependent upon recruitment into the parent clinical trial. Within this last year (and within 9 months of patient studies, Q1 was spent obtaining study approvals, setting up procedures, etc), we enrolled a total of 12 new participants. The plan is to enroll 2 participants/month into our neuroimaging study, for a total of 18 (or 19 per SOW) by the end of Year 1. The clinical trial is doing all they can to ramp up recruitment as described in their recent progress report and we expect that our recruitment will increase in parallel throughout next year. Proposed minor changes to inclusion/exclusion criteria will help these efforts as well.

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

See above.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

On May 4, 2016 we submitted a minor modification to UCSF/VA IRB, in which we request a minor change in the exclusion criteria. The change is to include participants from the clinical trial who have psychotic and/or bipolar related disorders. Many participants in the clinical trial exhibit psychotic and/or bipolar disorders and these types of comorbid conditions are representative of this study population. Inclusion of these participants will allow us to (a) achieve our enrollment target better; and (b) study a more representative sample of this population. The modification is in review. This minor modification will not require separate approval by the DoD.

6. PRODUCTS:

List any products resulting from the project during the reporting period.

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Name: Dieter J. Meyerhoff, Dr.rer.nat

Project Role: PI

Research Identifier:

Nearest person month worked: 2

Contribution to Project: Dr. Meyerhoff submits the regulatory materials to UCSF, the VA, and DoD. He has worked with Dr. Murray to study enrolled participants at the 3T, and he has overseen the set-up of the subject data base and the coordination efforts by the Research Associate with the clinical team around Dr. Batki. He oversees the activities of

Mr. Schmidt and Dr. Murray and actively participates in data acquisition. He is involved in efforts to get a new service contract in place for the 7T and is ready to do all necessary to get studies going at 7T.

Name: Donna Murray

Project Role: Postdoc

Research Identifier:

Nearest person month worked: 3

Contribution to Project: Dr. Murray has scanned research subjects and maintains the research data base. She sets up the obtained imaging data for semi-automated pipeline processing procedures. She also has assisted the PI in regulatory work, participated in coordinating procedures related to subject flow from the clinical trial into this research study.

Name: Thomas Schmidt

Project Role: Staff Research Associate III

Research Identifier:

Nearest person month worked: 1

Contribution to Project: Mr. Schmidt coordinates the recruitment of subjects with the parent clinical trial personnel. He is engaged in activities to streamline the procedures related to subject flow from the clinical trial into this research study and shepherds the research study participants through the study. He has also started to recruit controls for the study, who are studied in parallel with clinical trial patients. He also performs neurocognitive testing in the control participants, using a battery also administered to patients by clinical trial personnel.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Collaborators on this project are Drs. Steven Batki and David Pennington from VA Mental Health here in San Francisco, where the PTSD Program is headed by Dr. Thomas Neylan. Dr. Batki is the PI of the clinical trial, the parent study from which we recruit patients into this neuroimaging addendum. Dr. Pennington is the direct contact person for our neuroimaging study personnel; he helps facilitate recruitment and sharing of data between the projects.

8. SPECIAL REPORTING REQUIREMENTS:

QUAD CHARTS: The Quad Chart (available on <https://www.usamraa.army.mil>) shall be updated and submitted as an appendix.

See Appendix.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Nothing included, except updated Quad Chart.

Brain MR Spectroscopy Biomarkers in a Clinical Trial of Veterans with Alcohol Dependence and Co-Occurring PTSD

W81XWH-15-2-0020



PI: Dieter J. Meyerhoff, Dr.rer.nat.

Org: NCIRE

Award Amount: \$804,884 (directs+F&A)

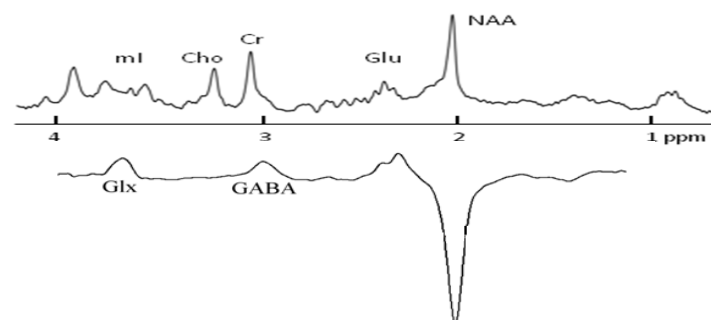
Study/Product Aim(s)

- Measure change of metabolite concentrations with study medication (topiramate and placebo) on 2 different MR scanners
- Relate metabolite concentration changes measured at 3 Tesla to changes in PTS symptoms and neurocognition
- Compare sensitivity of detection of metabolite changes measured on the different MR scanners

Approach

We will accomplish the specific aims by adding a neuroimaging component to an ongoing trial of topiramate for treatment of alcohol dependence in PTS disorder

- measuring metabolite levels at 3 Tesla (n = 40 patients) and at 7 Tesla (n = 20) before and after treatment with study medication
- test-retesting 10 healthy controls on both scanners
- measuring PTS symptoms, alcohol consumption, and neurocognition before and after treatment with study medication
- correlating MRS and neuropsychological measures in patients
- comparing MRS measures obtained from both scanners



We previously showed that 1H MR spectroscopy (MRS) can quantitate GABA, Glu, and NAA in alcohol dependence with and without PTS. These metabolite levels are related to insomnia severity, PTS symptoms, and drinking. In a pilot trial, topiramate treatment reduced PTS symptoms, alcohol craving, and drinking.

The proposed neuroimaging addendum to a definitive topiramate treatment trial will examine if topiramate facilitates functionally significant adaptive modulation of GABA and glutamate levels in the cortex of alcohol dependent PTS patients.

Timeline and Cost

Activities	CY	14	15	16	17
Initiate study: obtain IRB approvals, set up MR sequences at 7 Tesla					
Conduct data acquisition in patients and controls					
Conduct data processing and analyses					
Finalize analyses, perform statistics, disseminate results, complete final report, prepare data for DataShare, apply for future funding					
Estimated Budget (\$K)		152	152	336	165

Updated: 05/18/16

Goals/Milestones

CY14 Goal – Initiate Study

- ✓ Obtain IRB approvals.
- ✓ Prepare studies on 7T MR scanner

CY15 & CY 16 Goals – Conduct data acquisition, processing, analyses

- ☐ Acquire MRS data at 3T and 7T
- ☐ Process and compare MRS data from both scanners
- ☐ Analyze data and correlate 3T MRS data with neuropsych. data

CY17 Goal – Finalize, disseminate, futurize

- ☐ Finalize analyses, write manuscript(s), prepare DataShare, apply for future funding

Budget Expenditure to Date (as of 4/30/16)

Projected Expenditure: \$300K

Actual Expenditure: \$129,547 (directs+F&A)